

Poster Session I

these reports may be the result of publication bias, i.e., it appears that multiple groups have looked at this issue, but only those groups that have found a significant relationship, potentially as a result of random chance, have reported their findings. To further investigate this question we developed a multivariate logistic regression model for factors predictive of acute GVHD based on a series of 167 patients, including 18 African-Americans, who underwent allogeneic BMT at our institution between January 1, 1992 and May 30, 2004. Factors examined in the multivariate model included age, CD34 dose, CD3 dose, sex mismatch pattern (female-to-male vs other), category of conditioning regimen (full-dose vs reduced-dose), presence or absence of an antigen-level HLA mismatch, type of donor (related vs unrelated), stem cell source (marrow vs PBSC), and race (African-American vs Caucasian). It was not possible to separate out the potential effect of the GVHD prophylactic regimen because our data set is characterized by a very strong correlation between type of GVHD prophylactic regimen and category of conditioning regimen. We observed a univariate trend toward an increased incidence of Grade 3 or higher acute GVHD among African Americans (39% vs 21%, $p = 0.13$). Race was not independently predictive of acute GVHD in the multivariate model, although the statistical power of the model to detect this relationship was limited due to the fact that only 18 African Americans were included in the series. Interestingly, among patients transplanted since 1996, there was a statistically significant (univariate) increase in the incidence of grade 3 or higher acute GVHD among African Americans (64% vs 25%, $p = 0.01$) but also a parallel disparity in the incidence of HLA-mismatched transplantation (27% vs 6%, $p = 0.036$) such that race remained non-contributory in the multivariate model. We conclude that the purported relationship between race and acute GVHD may be less strong than has been previously reported due to publication bias and/or to an increased incidence of HLA-mismatched transplant in this population. Further examination of this issue using larger data sets appears warranted.

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EXTRACORPOREAL PHOTOCHEMOTHERAPY FOR (ECP) THE TREATMENT OF CHRONIC GRAFT-VERSUS-HOST DISEASE

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Introduction: Chronic graft-versus-host disease (cGVHD) is a major cause of long term morbidity and mortality following allogeneic hematopoietic stem cell transplant (HSCT). Beyond the combination of steroids and calcineurin inhibitors, a variety of immunosuppressive methods have been used to manage this condition, most of them of limited efficacy and steroid-sparing capacity. ECP is becoming increasingly used in the treatment of acute and chronic GVHD, with promising preliminary data. **Methods:** Retrospective evaluation of all ECP procedures performed between 1/30/98 and 10/2/92 in patients with GVHD occurring after day 100. Patients were considered evaluable for response when they were treated with ECP for at least 1 month, without the addition of any further immunosuppression. Complete (CR) and partial responses (PR) had a minimal duration of 2 weeks. **Results:** A total of 82 patients with chronic GVHD were analyzed. The median age was 40 (5–70), and the donor origin was matched sibling (48, 59%), matched unrelated (24, 29%) or mismatched (10) HSCT. Most of them received tacrolimus-based prophylaxis (74, 90%) and had a history of acute GVHD (64, 78%). Most patients were on steroids (64) and had received a median of 2 (1–6) treatments prior to ECP. Out of 82 patients, only 51 were evaluable for response, and the remainder received further immunosuppression within a month from the start of ECP (30), or lacked documentation (1). The CR/PR rate for evaluable patients was 82% ($n = 42$). Thirty-four patients (67%) had skin involvement and the majority (32, 94%) responded to ECP. All types of skin involvement (lichenoid, scleroderma, mixed, acute-appearing) responded to therapy. ECP also demonstrated activity in visceral GVHD, with response rates of (15, 88%) and (6, 67%) respec-

tively. The CR/PR rate for oral GVHD was 100% ($n = 6$), and for ocular GVHD 75% ($n = 3$). Of 51 patients, 32 required further immunosuppression for control of their GVHD. Since initiation of ECP, the overall survival for the whole group was 37%, with a median survival of 10 months. **Conclusions:** In this heavily pre-treated group of patients with chronic GVHD, the response to ECP seems promising in all organs, including GVHD of the lung and the liver. The prospective and systematic evaluation of the role of ECP in the management of GVHD is warranted.

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SUBEROYLANILIDE HYDROXAMIC ACID MODULATES THE INNATE AND ALLOSTIMULATORY RESPONSES OF DENDRITIC CELLS AND REGULATES EXPERIMENTAL ACUTE GRAFT-VERSUS-HOST DISEASE

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Dendritic cells modulate the innate (via Toll like receptors-TLRs) and the allostimulatory immune responses. Suberoylanilide hydroxamic acid (SAHA) is an anti-tumor agent that also exhibits potent anti-inflammatory properties. We investigated the effect of SAHA on modulating DC functions. Pre-incubation of BM derived DCs with 100 nM–500 nM concentrations of SAHA (s-DCs) significantly reduced the secretion of TNF- α and IL-6 upon TLR stimulation with lipopolysaccharide (TLR-4), peptidoglycan (TLR-2), poly IC (TLR-3) and CpG (TLR-9). Pre-treatment of DCs with SAHA significantly reduced the proliferation of allogeneic T cells in MLR cultures. Mixing experiments at 1:1 ratio significantly suppressed the allostimulatory capacity of control DCs. Incubation of DCs with SAHA significantly decreased the expression of CD40, CD80, CD86 and OX40L and but caused no significant changes in MHC class II expression. We determined the in vivo relevance of SAHA mediated effects on DCs by utilizing Class I disparate CD8⁺ mediated [bm1 \rightarrow β 2MG^{-/-}], and Class II disparate CD4⁺ mediated [bm12 \rightarrow MHC-II^{-/-}] murine models of alloreaction. Recipient β 2MG^{-/-} and Class-II^{-/-} B6 animals received 11 Gy, $2-4 \times 10^6$ T cells and 5×10^6 TCDBM cells from syngeneic B6 or allogeneic bm-1 and bm-12 donors respectively. The recipients were also injected on days -1 and 0 with $4-5 \times 10^6$ wild type B6 BM derived c-DC and s-DCs. Injection of s-DCs significantly reduced in vivo allogeneic donor T cell expansion of both CD4⁺ and CD8⁺ T cell subsets. We next utilized the well characterized mouse [BALB/c \rightarrow B6] model of acute GVHD to determine the effect of s-DCs on an ongoing GVHD reaction. On day -1, the recipient B6 animals received 11 Gy and on day 0 were injected with 2×10^6 T cells and 5×10^6 BM cells from syngeneic B6 or allogeneic BALB/c donors. Injection of 5×10^6 host type s-DCs on days -1, 0, and +2 resulted in significantly better survival, reduced serum levels of TNF- α , donor T cell expansion and histopathology of GVHD ($P < 0.01$) on day +7 after BMT. Lastly, we determined the effect of SAHA on the DCs derived from the peripheral blood of normal healthy human volunteers and found that SAHA significantly reduced allogeneic T cell proliferation. Together our results demonstrate that SAHA modulates innate and allostimulatory functions of DCs in vitro and in vivo, and suggest that SAHA treatment of DCs might represent a novel cellular therapy that can reduce clinical GVHD.

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MATURE T CELLS ALONE SEPARATE GVL FROM GVHD: THE NEED FOR BETTER CONTROLS

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Separation of graft-vs.-leukemia effect (GVL) from graft-vs.-host disease (GVHD) is the phenomenon that patients with leukemia/lymphoma achieve complete remission without GVHD after allogeneic stem cell transplantation. We demonstrate in this study that separation of GVL from GVHD could be achieved using only unmanipulated mature T cells in a mouse model. Graded numbers (10^3 – 10^6) of purified T cells from C57BL/6 mice were transplanted